

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

# 22q11 Deletion Syndrome: A Genetic Subtype of Schizophrenia

Anne S. Bassett and Eva W.C. Chow

NOTICE: THIS MATERIAL MAY BE PROTECTED BY COPYRIGHT LAW (TITLE 17 U.S. CODE)

*Schizophrenia is likely to be caused by several susceptibility genes and may have environmental factors that interact with susceptibility genes and/or nongenetic causes. Recent evidence supports the likelihood that 22q11 Deletion Syndrome (22qDS) represents an identifiable genetic subtype of schizophrenia. 22qDS is an under-recognized genetic syndrome associated with microdeletions on chromosome 22 and a variable expression that often includes mild congenital dysmorphic features, hypernasal speech, and learning difficulties. Initial evidence indicates that a minority of patients with schizophrenia (~2%) may have 22qDS and that prevalence may be somewhat higher in subpopulations with developmental delay. This paper proposes clinical criteria (including facial features, learning disabilities, hypernasal speech, congenital heart defects and other congenital anomalies) to aid in identifying patients with schizophrenia who may have this subtype and outlines features that may increase the index of suspicion for this syndrome. Although no specific causal gene or genes have yet been identified in the deletion region, 22qDS may represent a more homogeneous subtype of schizophrenia. This subtype may serve as a model for neurodevelopmental origins of schizophrenia that could aid in delineating etiologic and pathogenetic mechanisms. Biol Psychiatry 1999;46:882-891 © 1999 Society of Biological Psychiatry*

**Key Words:** Schizophrenia, genetics, subtype, neurodevelopment, chromosome 22, velocardiofacial syndrome

## Introduction

Schizophrenia is likely to be caused by several susceptibility genes (genetic heterogeneity) and may have environmental factors that interact with susceptibility genes or non-genetic causes (etiologic heterogeneity) (Kendler and Diehl 1993; McGuffin et al 1995). Various attempts have been made to reduce heterogeneity in

schizophrenia, primarily using clinical subtypes (Carpenter et al 1988) and sporadic/familial distinctions (Murray et al 1985). Recent evidence supports the likelihood that 22q11 Deletion Syndrome (22qDS) represents an identifiable genetic subtype of schizophrenia (Bassett et al 1998). This paper presents what is currently known about this syndrome, proposes clinical screening criteria, and outlines how this genetic subtype may serve as a neurodevelopmental model of schizophrenia and aid in delineating etiologic and pathogenetic mechanisms.

## 22q Deletion Syndrome (22qDS)

22qDS encompasses several genetic syndromes associated with microdeletions at chromosome 22q11.2, including velocardiofacial syndrome (VCFS) and DiGeorge syndrome (DGS) (Driscoll et al 1993; Kelly et al 1993; Lindsay et al 1995a; Scambler et al 1992). Learning disabilities, palatal anomalies, cardiac defects, and typical facial features are common, although the presentation is highly variable (Goldberg et al 1993; Shprintzen et al 1978; Shprintzen et al 1981; Yamagishi et al 1998). The syndrome was first described in the 1950s (Sedlackova 1967), delineated in the 1970s (Shprintzen et al 1978), and became more generally identified in pediatric populations in the 1990s through the availability of specialized chromosomal studies; routine karyotype analysis does not detect the deletion (Driscoll et al 1993; Lindsay et al 1995a). The estimated prevalence of the deletion is 1/4000 (du Montcel et al 1996), making 22qDS the second most common genetic syndrome after Down syndrome. 22qDS usually occurs as a sporadic mutation, but approximately 10% of cases are inherited from transmitting parents, who often have a less severe phenotype (Demczuk and Aurias 1995). Studies of 22qDS have usually involved infants and children because ascertainment has mainly been through pediatric specialty clinics. The variability of the phenotype and limited knowledge of the syndrome by medical practitioners mean that 22qDS remains largely undiagnosed, especially in adults where later onset behavioural manifestations may become prominent features.

From the Schizophrenia Research Program, Centre for Addiction & Mental Health, Queen Street Division and Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada.

Address reprint requests to Dr. Anne Bassett, Schizophrenia Research Program, Centre for Addiction & Mental Health, Queen Street Division, 1001 Queen Street West, Toronto, Ontario M6J 1H4, Canada.

Received October 2, 1998; revised February 25, 1999; revised May 3, 1999; accepted May 4, 1999.

Table 1. Screening Criteria to Identify Patients with Schizophrenia at Increased Risk for 22q Deletion Syndrome

Two or more of the following features<sup>a</sup>

1. Hypernasal speech, history of speech therapy, velopharyngeal incompetence, cleft palate (usually submucosal)
2. Characteristic facial features: e.g., long, narrow face, narrow palpebral fissures, flat cheeks, prominent nose, small ears, small mouth, retruded chin
3. Learning difficulties, history of special education, mental retardation (borderline to mild)
4. Congenital heart defect: e.g., ventricular septal defect, tetralogy of Fallot, right aortic arch, double aortic arch
5. Other significant congenital anomaly: e.g., talipes (club foot), polydactyly (extra finger or toe), kyphosis/scoliosis, renal anomaly, hypospadias
6. History of hypocalcemia (neonatal, childhood, adolescence or adult onset) and/or hypoparathyroidism
7. History of athymia (absent thymus gland) or severe immune deficiency in infancy

<sup>a</sup>The 22qDS phenotype is variable. Examples are provided of features reported in adults with schizophrenia; specific features listed may not be present or others may be identified in an individual patient.

## Schizophrenia and Other Psychiatric Disorders in 22qDS

Researchers have reported a high prevalence of serious psychiatric illnesses in adult patients with 22qDS (Papoulos et al 1996; Pulver et al 1994; Shprintzen et al 1992). In a study of 40 adults with 22qDS, the most common psychiatric disorder found on direct interview using DSM-IV criteria was schizophrenia (25%), followed by major depression (13%) and bipolar disorder (2.5%) (Murphy and Owen 1997). Four (31%) of 13 adults with 22qDS in another study had DSM-III-R schizophrenia or schizoaffective disorder (Pulver et al 1994). In contrast, there is no evidence of elevated rates of schizophrenia in other genetic syndromes with behavioral phenotypes (Turk and Hill 1995), and there are only mildly elevated rates of schizophrenia (~3%) in mental retardation (Turner 1989). The high rate of schizophrenia in 22qDS also does not appear to be related to major psychotic illness in first or second degree relatives (Bassett et al 1998; Pulver et al 1994). These early studies suggest that morbid risk of schizophrenia for a patient with 22qDS may be approximately 25 times the general population risk, and double the risk of a first degree relative of an individual with schizophrenia.

## 22qDS as a Subtype of Schizophrenia

Although there are no large scale epidemiologic studies of 22qDS yet available in psychiatric samples, the available evidence suggests that a small but significant subset of patients with schizophrenia may have this syndrome. One study found 22q11.2 deletions in 2 of 100 random patients with schizophrenia screened for the deletion; minor facial features were subsequently identified in the deleted patients (Karayiorgou et al 1995). Consistent with this prevalence figure, a recent study of 32 well characterized subjects with childhood onset schizophrenia found 1 subject (3%) with a 22q11 deletion (Yan et al 1998). Subjects with IQ <70 were not included in either of these

studies. The rate of detecting the deletion however may be higher in adults with a dual diagnosis of schizophrenia and developmental disabilities. One study found 22qDS in 2 (9%) of 22 such subjects (Murphy et al 1998). These preliminary studies indicate that the rate of 22qDS in schizophrenia may be approximately 80 times the estimated general population rate of 22q11.2 deletions (1/4,000) (du Montcel et al 1996). These compelling early findings have led to the proposal that 22qDS is a genetic subtype of schizophrenia (Bassett et al 1998; Propping and Nothen 1995).

## Identifying 22qDS in Schizophrenia

Several groups (Bassett et al 1998; Gothelf et al 1997; Murphy et al 1998) have shown that 22qDS may be identified in clinical populations with schizophrenia who are screened for the presence of common syndromal features (see Table 1 for proposed clinical screening criteria). Age at onset, psychotic symptoms, and comorbid symptoms are consistent with those usually found in schizophrenia (Bassett et al 1998; Gothelf et al 1997; Pulver et al 1994). Behavioral and mood features (such as anxiety, depression, temper/aggressive outbursts, impulsive and compulsive behavior) observed in 22qDS-schizophrenia (Bassett et al 1998; Pulver et al 1994) are also commonly observed in schizophrenia (Häfner and an der Heiden 1997; Russell et al 1997). Although few data are yet available for adults with 22qDS, intellect appears to be most commonly in the borderline mental retardation range, with some subjects having low average intellect and a minority having mild mental retardation (Bassett et al 1998). This suggests that intellectual deficits may, in general, be more severe in a 22qDS subtype of schizophrenia. Comprehensive neuropsychological studies are needed to clarify whether the pattern of cognitive deficits is similar to that commonly found in schizophrenia (Green 1996).

Findings related to a neurodevelopmental hypothesis for

schizophrenia and from genetic studies of schizophrenia provide further supportive evidence for a 22qDS subtype of schizophrenia.

### Supportive Evidence: Neurodevelopmental

An observed increased prevalence of minor physical abnormalities (Green et al 1989; Guy et al 1983; O'Callaghan et al 1991) is considered supportive of a neurodevelopmental origin for schizophrenia (Murray and Lewis 1987; Weinberger 1997). In addition to major features (see Table 1), minor dysmorphic features are common in 22qDS (Bassett et al 1998; Goldberg et al 1993; Lipson et al 1991). Several of these, such as high arched palate, overlap with the minor physical abnormalities usually assessed in studies of schizophrenia (Green et al 1989; Griffiths et al 1998; Guy et al 1983; O'Callaghan et al 1991). Interestingly, physical features seen in 22qDS are similar to many of those listed by Kraepelin (Kraepelin 1971) as common in schizophrenia: "small stature, youthful appearance, malformation of the cranium and of the ears, high and narrow palate, persistence of the intermaxillary bone, abnormal growth of hair, strabismus, deformities of the fingers or toes, polymastia, defective development and irregularity of the teeth."

Developmental abnormalities reported to be elevated in the premorbid phase of schizophrenia also support a neurodevelopmental origin for schizophrenia (Done et al 1994; Jones et al 1994). These include developmental delays, speech difficulties, minor coordination deficits, blunted affect, and social withdrawal (Done et al 1994; Jones et al 1994). Similar features have also been reported to be prevalent in children with 22qDS (Golding-Kushner et al 1985; Haapanen and Somer 1993). One of the most common features in children with 22qDS is an intellectual deficit that results in decreased educational achievement (Golding-Kushner et al 1985; Kok and Solman 1995; Swillen et al 1997). Similarly, childhood cognitive deficits are significant features in schizophrenia and are considered further evidence of a neurodevelopmental origin for schizophrenia (Done et al 1994; Jones et al 1994).

Structural brain abnormalities are relatively frequent in schizophrenia and may be found at onset of illness, further supporting a neurodevelopmental hypothesis of schizophrenia (Weinberger 1997). Commonly reported brain anomalies include mild cortical atrophy, ventricular enlargement, decreased gray matter, and increased prevalence of midline developmental abnormalities, such as cavum septum pellucidum or cavum vergae (Degreef et al 1992; Johnstone et al 1976; Lewis and Mezey 1985; Zipursky et al 1998; Zipursky et al 1992). Preliminary results indicate similar anomalies in a 22qDS subtype of schizophrenia (Chow et al in press; Chow et al 1999) as

well as increased hyperintensity signals, radiologic findings of unknown origin (Marsh et al 1996), that may be more specific to the subtype. Comparable findings have been reported in small studies involving mostly children with 22qDS (Haapanen and Somer 1993; Mimick et al 1996; Mitnick et al 1994).

Syndromes with facial abnormalities are often associated with neurologic or psychiatric abnormalities (Winter 1996). This may be because facial development is dependent upon prosencephalic and rhombencephalic organizing centres or because specific genes are important both in the developing brain and face (Winter 1996). 22qDS is thought to originate during embryonic development. The pathogenesis has been hypothesized to involve abnormal neural crest cell migration (Demczuk and Aurias 1995; Mansour et al 1987; Nickel et al 1994; Scambler et al 1992; Thomas and Frias 1987). This proposed pathogenetic mechanism for 22qDS may overlap with the abnormal neuronal migration and other abnormalities of early neurodevelopment posited for schizophrenia (Bassett et al 1998; Bogerts 1993; Chow et al 1994; Weinberger 1987).

### Supportive Evidence: Genetic

Like schizophrenia (Gottesman and Shields 1982), 22qDS most commonly presents as a sporadic occurrence in families, originating with a *de novo* mutation in the majority of cases (Dallapiccola et al 1996). 22qDS is inherited by autosomal dominant transmission in only about 10% of cases (Dallapiccola et al 1996; Lévy et al 1997). Interestingly, increased minor physical abnormalities have recently been reported to be more prevalent in "sporadic" schizophrenia (Griffiths et al 1998). Consistent with family and twin studies of schizophrenia that indicate reduced penetrance and variable expression, (Kendler and Diehl 1993), the psychiatric phenotype in 22qDS appears to be associated with schizotypal features and psychiatric disorders other than schizophrenia, including schizoaffective disorder, major depression and bipolar disorder (Murphy and Owen 1997; Papolos et al 1996; Pulver et al 1994). Affective disorders do not appear to be as prevalent as schizophrenia in adults (Murphy and Owen 1997; Pulver et al 1994) but may occur as early manifestations in an evolving psychiatric phenotype (Papolos et al 1996). This may be comparable to depressive features that often appear early in a first psychotic episode of schizophrenia (Lieberman 1995).

With respect to genetic linkage studies of schizophrenia, there are weak linkage findings implicating the 22q12 region (Schizophrenia Collaborative Linkage Group for Chromosome 22 1998), several million base pairs distal to the 22q11.2 deletion region. Nonsignificant LOD scores despite large sample sizes suggest that few families may

be linked or a mutation in a susceptibility gene or genes located on distal chromosome 22 may have a small effect (Moldin and Gottesman 1997), consistent with the genetic heterogeneity expected in schizophrenia. Also, linkage studies use families with two or more affected relatives, most often siblings. Individuals with schizophrenia in these studies would therefore be particularly unlikely to have 22qDS since the deletion usually occurs as a sporadic mutation.

## Molecular Background on 22qDS

### 22q11.2 Microdeletion

The fluorescence in-situ hybridization (FISH) technique uses a fluorescently labeled probe from the 22q11.2 region to unequivocally identify chromosomes that do not fluoresce, i.e., those with submicroscopic deletions (Karayiorgou et al 1995; Kucherlapati et al 1995; Lindsay et al 1995a). FISH has therefore come to play a major role in clinical laboratory testing for microdeletions (Hall 1993). About 80% of patients with VCFS or related syndromes are found to have a 22q microdeletion; there are three main types (Kurahashi et al 1996; Morrow et al 1995). The largest (type 1) is the most common, with an estimated deletion size of 2-3 megabases (Mb). A smaller deletion (type 2) overlaps the proximal region of type 1 deletions. The D22S75 (N25) marker commonly used in clinical diagnostic FISH laboratories to diagnose the 22q microdeletion maps to the region overlapped by types 1 and 2 deletions (Morrow et al 1995), both of which have been reported in schizophrenia (Karayiorgou et al 1995). A third smaller deletion (type 3) that appears to overlap with the distal end of the largest deletion is very rare and requires a different probe for detection (Kurahashi et al 1996). The monosomy, or reduced dosage of genes within the 22q11.2 deleted region, is believed to cause the 22qDS phenotype.

### Candidate Genes

There are many interesting candidate genes in the 22q11.2 region. One of these, catechol-*O*-methyltransferase (COMT), is an enzyme involved in catecholamine inactivation. Studies indicate that there is no allelic association with schizophrenia (Daniels et al 1996) and both low and high activity COMT alleles occur in adult patients with 22q11 deletions and psychosis (Lachman et al 1996). There is preliminary evidence for the role of the low activity form of this gene in violent behavior (Lachman et al 1998). Other genes of interest in the deletion region include: TUPLE1, a transcription factor (Halford et al 1993); DGCR2, an adhesion receptor protein (Budarf et al 1995; Demczuk et al 1995), CLTD, a clathrin heavy chain gene (Sirotkin et al 1996); TMVCF, a transmembrane

protein (Sirotkin et al 1997), and a developmentally expressed ubiquitination gene (Pizzuti et al 1997). Some of these have been found by screening fetal brain cDNA libraries. No point mutations have been detected in the candidate genes identified to date, even those disrupted by translocation breakpoints. This suggests that disruption of a sequential group of genes, perhaps involving disruption of regional regulation, is more likely than a single gene in causing 22qDS (Kurahashi et al 1996; Sutherland et al 1996).

### Etiologic Heterogeneity

Approximately 20% of patients with syndromal features do not have a detectable deletion using the D22S75 probe (Carlson et al 1997; Lindsay et al 1995a; Morrow et al 1995). This indicates that in a minority of patients there are likely to be other causes of the syndrome, possibly involving point mutations in key genes in the 22q11 region that have yet to be identified (Lindsay et al 1995a). Other chromosomal regions, including 10p13 and 18q21, have been associated with some DGS features (Daw et al 1996; Greenberg 1993; Monaco et al 1991) but facial features appear to be different (Demczuk and Aurias 1995). Non-genetic causes of syndromal features are also possible (Hall 1993). These include exposure during pregnancy to teratogens such as alcohol and retinoids (Nickel et al 1994), that can cause similar appearing phenotypes, possibly because of effects on neural crest cell migration in embryonic development (Demczuk and Aurias 1995). Interestingly, a recent study of adults with fetal alcohol syndrome and fetal alcohol effects indicates an increased prevalence of psychotic disorders (Famy et al 1998).

### Clinical Heterogeneity

The phenotype is highly variable both between and within families (Leana-Cox et al 1996; Lindsay et al 1995a; Lipson et al 1991; McLean et al 1993; Meinecke et al 1986), even when the same molecular genetic defect is apparently present (Motzkin et al 1993). Monozygotic (identical) twins with VCFS have also been reported to have variable phenotypes (Fryer 1996; Hatchwell 1996). There is no apparent correlation between the severity or pattern of the expressed phenotype and the extent of the deletion for 22qDS (Carlson et al 1997). The factors responsible for the phenotypic diversity are unknown, but are likely to involve variability in the many genes expressed on the normal 22q11.2 chromosomal segment (Demczuk and Aurias 1995; Sirotkin et al 1996). Interacting or additive environmental factors such as teratogens, somatic mosaicism (e.g., deletions in some cells and not others) (Pinto-Escalante et al 1998) or stochastic (chance) effects could also play a role in clinical heterogeneity.

## Developing an Index of Suspicion for 22qDS in Adults with Schizophrenia

A high index of suspicion and a careful clinical assessment should help to identify patients with schizophrenia and a 22q11 deletion, as has been shown in populations of patients with cleft palate (Mingarelli et al 1996) and cardiac defects (Amati et al 1995). The best features to use in screening adult populations have yet to be determined. Several studies suggest that patients with features of variable severity from 2 or 3 of the systems usually involved in 22q11 deletion syndromes, especially minor dysmorphic features and hypernasal speech, are likely to carry the deletion (Bassett et al 1998; Finkelstein et al 1993; Goldberg et al 1993; Gothelf et al 1997; Lipson et al 1991; Ravnar et al 1996) (see Table 1). Nonsyndromic patients with only one feature, such as cleft palate (Debrus et al 1996; Mingarelli et al 1996) or congenital heart defect (Amati et al 1995; Takahashi et al 1995), do not appear to have associated 22q11 deletions. Careful examination for congenital features is essential, since some phenotypic features may be influenced by age (Jones 1997) or antipsychotic medications. For example, hypotonia could be obscured and kyphosis and scoliosis may be worsened by the parkinsonian side effects of conventional antipsychotic medications.

Using medical history and a standardized physical examination for 103 minor dysmorphic features (SPEDF) developed by our group, we have demonstrated that we can identify 22qDS in adult patients with schizophrenia who meet clinical referral criteria (Bassett et al 1998). In 9 (32%) of 28 patients with schizophrenia referred from psychiatric sources who had two or more of the features outlined in Table 1, FISH studies using a standard probe at locus D22S75 confirmed a 22q11.2 deletion (unpublished data). These preliminary results represent a 16-fold increase in deletion detection over the prior probability of approximately 2% (Karayiorgou et al 1995). Although subjects with a 22q11.2 deletion had a greater total number of minor dysmorphic features than non-deleted subjects, no one feature was pathognomonic for deleted subjects (unpublished data). Further studies are needed to determine a set of clinical screening criteria for 22qDS with high sensitivity, specificity, and positive predictive value.

Developmental, medical, and family histories may be useful adjuncts in identifying patients who may have 22qDS. Developmental medical history may include neonatal seizures due to hypocalcemia that is secondary to hypoparathyroidism (Cuneo et al 1997), or repeated infections, due to defective cellular immunity. These features, typical of DGS, occur most often in infants and children and are usually transient (Goldberg et al 1993; Lindsay et al 1995b; Ravnar et al 1996). Any system may be

affected, including musculoskeletal, renal, gastrointestinal, and haematologic (e.g., thrombocytopenia [low platelets]) (Lévy et al 1997; Ryan et al 1997). In the case of a transmitted deletion, the family history may include siblings with early infant death or stillbirth. Features to consider are shown in Table 2.

## Clinical Considerations

There are several clinical imperatives to consider if 22qDS is diagnosed in an adult patient. First, patients with 22qDS will benefit from a consultation with a medical geneticist. Ongoing monitoring for onset of associated psychiatric illness, hypocalcemia, and hypothyroidism, that may occur in later years, has been recommended (Bassett et al 1998; Cuneo et al 1997). These are treatable conditions and patients would benefit from early diagnosis and treatment that could lead to improved long-term outcomes. There is supportive evidence for this in schizophrenia (Lieberman 1995). Other medical conditions, such as cerebellar degeneration (Lynch et al 1995) may also be later occurring features of 22qDS. There are no published data on late-life or long-term outcome in 22qDS. Second, the 22qDS patients, and possibly family members should be offered genetic counseling (Driscoll et al 1993; Ryan et al 1997). 22qDS demonstrates autosomal dominant transmission, therefore patients with the syndrome have a 50% risk of passing on the deletion to offspring. Counseling is difficult because of the variability of the phenotype and there are no data yet on the likelihood of transmitting individual features, including psychiatric disorders. Reproductive fitness is likely to be unaffected by the syndrome in many cases; adults with 22qDS are often identified because they have had children severely affected with 22qDS (Leana-Cox et al 1996). As part of standard clinical recommendations, parents of patients identified to have a 22q11.2 deletion should be tested to determine if the deletion was transmitted (Ryan et al 1997). Third, receiving a genetic diagnosis may relieve parents of guilt or inappropriate blame for causing behavioral manifestations of the condition, and families may further benefit from 22qDS peer support networks, where available (Turk and Hill 1995).

## Research-Related Advantages of Identifying a 22qDS Subtype of Schizophrenia

Schizophrenia has usually been subtyped on the basis of symptom patterns (e.g., paranoid, disorganized, catatonic; or deficit syndrome) (Carpenter et al 1988) or familial (considered more genetic) and "sporadic" (considered

Table 2. History and Physical Examination Features<sup>a,b</sup> That Should Increase the Index of Suspicion for 22q Deletion Syndrome

Physical examination (limited) <sup>b</sup>	Neuropsychiatric features	Family history	Developmental history	Medical history	Laboratory
Hypomastic speech	Borderline to mild mental retardation	Miscarriages, stillbirths, early infant deaths, congenital heart defects (especially siblings)	Neonatal convulsions	Palatal repair of velopharyngeal insufficiency or cleft	Low calcium
Different looking facial features (long, narrow face, small chin, narrow or slanted palpebral fissures, prominent nose, small mouth, small ears)	Temper outbursts	Learning or speech difficulties	Difficulties feeding	Congenital heart defect such as ventricular septal defect, right-sided aortic arch, tetralogy of Fallot	Low platelet count
Slender, tapered fingers	Preservative speech	Note: usually no history of psychosis	Repeated infections	Any other congenital defect	
Scoliosis or kyphosis	Compulsive behavior		Developmental delays especially speech delay		
Any congenital anomaly (e.g., talipes [club foot])	Hearing deficit		Speech therapy		
Height different from siblings			Learning difficulties or special education		
			Absence of alcoholism or high dose retinoic acid during gestation		

<sup>a</sup>Individual features are nonspecific; a pattern of several features may warrant a referral to medical genetics.

<sup>b</sup>Features are congenital, not acquired.

relatively nongenetic or more environmental), based on family history of schizophrenia (Murray et al 1985). The principal rationale for subtyping is to reduce heterogeneity in the syndrome, and determine clinically meaningful divisions that have prognostic or etiologic significance. Identifying a 22qDS subtype of schizophrenia may have several advantages.

First, a 22qDS subtype could serve as a neurodevelopmental model for schizophrenia and could therefore lead to a better understanding of pathogenesis. This would include an enhanced ability to determine environmental risk factors that interact with genetic risk. Studies involving a 22qDS subtype could clarify neurodevelopmental mechanisms by helping to determine which factors considered to be due to environmental insults, such as minor physical abnormalities (Cannon and Murray 1998), are more likely to be secondary to abnormal fetal development of genetic origin. Also, knowledge about a 22qDS subtype of schizophrenia may be useful to reexamine results from studies investigating "sporadic" schizophrenia, as this term may pertain to subjects with a genetic etiology.

Second, identifying a genetic subtype of schizophrenia would be an important first step in reducing the heterogeneity associated with the disorder. Investigations of subjects with an etiologically homogeneous form of the disorder could reduce the usually high variance associated with virtually any measure. If specific clinical parameters, such as symptoms, course and treatment response, were found to be different in a 22qDS subtype from other

patients with schizophrenia, this could have significant bearing on predicting outcome. Alternatively, if clinical features were found to be as variable in 22qDS as they are in other forms of schizophrenia this may suggest similar mechanisms for clinical heterogeneity. Other areas of research, such as imaging and neurophysiological studies, could also benefit from the potential reduction in heterogeneity conveyed by identification of a subtype. Many existing studies may screen 22qDS patients out with criteria that exclude patients with learning difficulties or associated medical conditions.

Third, ascertaining patients with a 22qDS subtype of schizophrenia could prove important in the search for genetic etiologies of schizophrenia. Genes located in the 22q11.2 deletion region may be involved in causing schizophrenia in some cases. A deletion provides a physical location for disease genes that statistical linkage studies of this complex disorder cannot. Localizing one gene for even a rare subtype of schizophrenia could lead to identification of related genes relevant to more common subtypes of the illness. Down Syndrome (DS), which is usually caused by trisomy of chromosome 21, provides a model for such an approach. The finding of a late-occurring psychiatric manifestation in DS, dementia of the Alzheimer type (AD), helped lead to the discovery of a gene (amyloid precursor protein) located on chromosome 21 which is involved in causing a rare form of familial AD (Masters et al 1985; Wisniewski et al 1985). Alternatively, a 22q11.2 gene may interact with another gene on chro-



mosome 22q, within the deletion region or outside it, or on another chromosome, to cause schizophrenia.

## Conclusion

A 22qDS subtype of schizophrenia is an important but currently under-recognized entity. The means are now at hand to begin to identify patients with this subtype. Many investigations are needed to determine the relationship of a 22qDS subtype to the heterogeneous entity known as schizophrenia. These will involve studies of symptom patterns, associated psychiatric disorders, cognitive deficits, structural and functional brain abnormalities, clinical and molecular epidemiology, and eventually etiology and pathogenesis. An identifiable subtype with potential importance for delineating a genetic etiology and neurodevelopmental mechanisms of schizophrenia provides an exciting opportunity for researchers and clinicians.

Financial support received from: Ontario Mental Health Foundation, Scottish Rite Schizophrenia Research Program, and National Alliance for Research on Schizophrenia and Depression (Independent Investigator Award and Young Investigator Award).

This work was presented at the conference, "Schizophrenia: From Molecule to Public Policy" held in Santa Fe, New Mexico in October 1998. The conference was sponsored by the Society of Biological Psychiatry through an unrestricted educational grant provided by Eli Lilly and Company.

## References

- Arnati F, Mari A, Digilio MC, et al (1995): 22q11 deletions in isolated and syndromic patients with tetralogy of Fallot. *Hum Genet* 95:479-482.
- Bassett AS, Hodgkinson K, Chow EWC, Correia S, Scutt L, Weksberg R (1998): 22q11 deletion syndrome in adults with schizophrenia. *Am J Med Genet* 81:328-337.
- Bogerts B (1993): Recent advances in the neuropathology of schizophrenia. *Schizophr Bull* 19:431-445.
- Budarf ML, Collins J, Gong W, et al (1995): Cloning a balanced translocation associated with DiGeorge syndrome and identification of a disrupted candidate gene. *Nature Genet* 10:269-277.
- Cannon M, Murray RM (1998): Neonatal origins of schizophrenia. *Arch Dis Child* 78:1-8.
- Carlson C, Sirotkin H, Pandita R, et al (1997): Molecular definition of 22q11 deletions in 151 velo-cardio-facial syndrome patients. *Am J Hum Genet* 61:620-629.
- Carpenter WT, Heinrichs DW, Wagman AMI (1988): Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry* 145:578-583.
- Chow EWC, Mikulis D, Scutt L, Zipursky RB, Weksberg R, Bassett AS (in press): Qualitative MRI findings in adults with 22q11 deletion syndrome and schizophrenia. *Biol Psychiatry*.
- Chow E, Zipursky RB, Mikulis D, Scutt L, Weksberg R, Bassett AS (1999): MRI findings in adults with 22q11 deletion syndrome (22qDS) and schizophrenia. *Schizophr Res* 36:89.
- Chow EWC, Bassett AS, Weksberg R (1994): Velo-cardio-facial syndrome and psychotic disorders: implications for psychiatric genetics. *Am J Med Genet* 54:107-112.
- Cunéo BF, Driscoll DA, Gidding SS, Langman CB (1997): Evolution of latent hypoparathyroidism in familial 22q11 deletion syndrome. *Am J Med Genet* 69:50-55.
- Dallapiccola B, Pizzuti A, Novelli G (1996): How many breaks do we need to CATCH on 22q11? *Am J Hum Genet* 59:7-11.
- Daniels JK, Williams NM, Williams J, et al (1996): No evidence for allelic association between schizophrenia and a polymorphism determining high or low catechol-O-methyltransferase activity. *Am J Psychiatry* 153:268-270.
- Daw SCM, Taylor C, Kramau M, et al (1996): A common region of 10p deleted in DiGeorge and velocardiofacial syndromes. *Nature Genet* 13:458-460.
- Debrus S, Berger G, de Meeus A, et al (1996): Familial non-syndromic conotruncal defects are not associated with a 22q11 microdeletion. *Hum Genet* 97:138-144.
- Degreef G, Ashtari M, Bogerts B, et al (1992): Volumes of ventricular system subdivisions measured from magnetic resonance images in first-episode schizophrenic patients. *Arch Gen Psychiatry* 49:531-537.
- Demczuk S, Aledo R, Zucman J, et al (1995): Cloning of a balanced translocation breakpoint in the DiGeorge syndrome critical region and isolation of a novel potential adhesion receptor gene in its vicinity. *Hum Mol Genet* 4:551-558.
- Demczuk S, Aurias A (1995): DiGeorge syndrome and related syndromes associated with 22q11.2 deletions: a review. *Annales de Genetique* 38:59-76.
- Done DJ, Crow TJ, Johnstone EC, Sacker A (1994): Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. *Brit Med J* 309:699-703.
- Driscoll DA, Salvin J, Sellinger B, et al (1993): Prevalence of 22q11 microdeletions in DiGeorge and velocardiofacial syndromes: implications for genetic counselling and prenatal diagnosis. *J Med Genet* 30:813-817.
- du Montcel ST, Mendizabal H, Ayme S, Levy A, Philip N (1996): Prevalence of 22q11 microdeletion. *J Med Genet* 33:719.
- Famy C, Streissguth AP, Unis AS (1998): Mental illness in adults with fetal alcohol syndrome or fetal alcohol effects. *Am J Psychiatry* 155:552-554.
- Finkelstein Y, Zohar Y, Nachmani A, et al (1993): The otolaryngologist and the patient with velocardiofacial syndrome. *Arch Otolaryngol Head Neck Surg* 119:563-569.
- Fryer A (1996): Monozygotic twins with 22q11 deletion and discordant phenotypes. *J Med Genet* 33:261-264.
- Goldberg R, Motzkin B, Marion R, Scambler PJ, Shprintzen RJ (1993): Velo-cardio-facial syndrome: a review of 120 patients. *Am J Med Genet* 45:313-319.
- Golding-Kushner KJ, Weller G, Shprintzen RJ (1985): Velo-cardio-facial syndrome: language and psychological profiles. *J Craniofacial Gen Dev Biol* 5:259-266.
- Gothelf D, Frisch A, Munitz H, et al (1997): Velocardiofacial manifestations and microdeletions in schizophrenic patients. *Am J Med Genet* 72:455-461.



## 22q11 Deletion Syndrome

BIOL PSYCHIATRY  
1999;46:882-891

889

- Gottesman II, Shields J (1982): *Schizophrenia: The Epigenetic Puzzle*. Cambridge: Cambridge University Press.
- Green MF (1996): What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 153:321-329.
- Green MF, Satz P, Galer DJ, Ganzell S, Kharabi F (1989): Minor physical anomalies in schizophrenia. *Schizophr Bull* 15:91-99.
- Greenberg F (1993): DiGeorge syndrome: An historical review of clinical and cytogenetic features. *J Med Genet* 30:803-806.
- Griffiths TD, Sigmundsson T, Takei N, et al (1998): Minor physical anomalies in familial and sporadic schizophrenia: the Maudsley family study. *J Neurosurg Psychiatry* 64:56-60.
- Guy JD, Majorski LV, Wallace CJ, et al (1983): The incidence of minor physical anomalies in adult male schizophrenics. *Schizophr Bull* 9:571-582.
- Haapanen ML, Somer M (1993): Velocardiofacial syndrome: analysis of phoniatric and other clinical findings. *Folia Phoniatrica* 45:239-246.
- Häfner H, an der Heiden W (1997): Epidemiology of schizophrenia. *Can J Psychiatry* 42:139-151.
- Halford S, Lindsay E, Nayudu M, Carey AH, Baldini A, Scambler PJ (1993): Lowcopy-number repeat sequences flank the DiGeorge/velo-cardio-facial syndrome loci at 22q11. *Hum Mol Gene* 2:191-196.
- Hall JG (1993): CATCH 22. *J Med Genet* 30:801-802.
- Hatchwell E (1996): Monozygotic twins with chromosome 22q11 deletion and discordant phenotype. *J Med Genet* 33:261-264.
- Johnstone EC, Crow TJ, Frith DC, Husband J, Kreel L (1976): Cerebral ventricular size and cognitive impairment in schizophrenia. *Lancet* 2:924-926.
- Jones KL (1997): *Smith's Recognizable Patterns of Human Malformation*, 5th ed. Philadelphia: WB Saunders.
- Jones P, Rodgers PB, Murray RM, Marmot M (1994): Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet* 344:1398-1402.
- Karayorgou M, Morris MA, Morrow B, et al (1995): Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. *Proc Nat Acad Sci U S A* 92:7612-7616.
- Kelly D, Goldberg R, Wilson D, et al (1993): Confirmation that the velo-cardio-facial syndrome is associated with haploinsufficiency of genes at chromosome 22q11. *Am J Med Genet* 45:308-312.
- Kendler KS, Diehl SR (1993): The genetics of schizophrenia: a current, genetic-epidemiologic perspective. *Schizophr Bull* 19:261-284.
- Kok LL, Solman RT (1995): Velocardiofacial syndrome: learning difficulties and intervention. *J Med Genet* 32:612-618.
- Kraepelin E (1971): *Demencia Praecox and Paraphrenia*, Fascimile 1919 edition ed. Huntington, New York: Robert E. Krieger Publishing Co. Inc.
- Kucherlapati RS, Shprintzen RJ, Baldini A (1995): Velo-cardio-facial syndrome: frequency and extent of 22q11 deletions. *Am J Med Genet* 57:514-522.
- Kurahashi H, Nakayama T, Osugi Y, et al (1996): Deletion mapping of 22q11 in CATCH22 syndrome: identification of a second critical region. *Am J Hum Genet* 58:1377-1381.
- Lachman HM, Morrow B, Shprintzen R, et al (1996): Association of codon 108/158 catechol-O-methyltransferase gene polymorphism with the psychiatric manifestations of velo-cardio-facial syndrome. *Am J Med Genet* 67:468-472.
- Lachman HM, Nolan KA, Mohr P, Saito T, Volavka J (1998): Association between catechol-O-methyltransferase genotype and violence in schizophrenia and schizoaffective disorder. *Am J Psychiatry* 155:835-837.
- Leana-Cox J, Pangkanon S, Eanet KR, Curtin MS, Wulfsberg EA (1996): Familial DiGeorge/velocardiofacial syndrome with deletions of chromosome area 22q11.2: report of five families with a review of the literature. *Am J Med Genet* 65:309-316.
- Lévy A, Michel G, Lemerrer M, Philip N (1997): Idiopathic thrombocytopenic purpura in two mothers of children with DiGeorge sequence: a new component manifestation of deletion 22q11? *Am J Med Genet* 69:356-359.
- Lewis S, Mezey G (1985): Clinical correlates of septum pellucidum cavities—an unusual association with psychosis. *Psychol Med* 15:43-54.
- Lieberman JA (1995): Signs and symptoms: what can they tell us about the clinical course and pathophysiologic processes of schizophrenia? *Arch Gen Psychiatry* 52:361-363.
- Lindsay EA, Goldberg R, Jurecic V, et al (1995a): Velo-cardio-facial syndrome: frequency and extent of 22q11 deletions. *Am J Med Genet* 57:514-522.
- Lindsay EA, Greenberg F, Shaffer LG, Shapira SK, Scambler PJ, Baldini A (1995b): Submicroscopic deletions at 22q11.2: variability of the clinical picture and delineation of a commonly deleted region. *Am J Med Genet* 56:191-197.
- Lipson AH, Yuille D, Angel M, Thompson PG, Vandervoort JG, Beckebam EJ (1991): Velocardiofacial (Shprintzen) syndrome: an important syndrome for the dysmorphologist to recognise. *J Med Genet* 28:596-604.
- Lynch DR, McDonald-McGinn DM, Zackai EH, et al (1995): Cerebellar atrophy in a patient with velocardiofacial syndrome. *J Med Genet* 32:561-563.
- Mansour AM, Goldberg RB, Wang FM, Shprintzen RJ (1987): Ocular findings in the velo-cardio-facial syndrome. *J Pediatr Ophthalmol Strabismus* 24:263-266.
- Marsh L, Lauriello J, Sullivan E, Pfefferbaum A (1996): Neuroimaging in psychiatric disorders. In: Bigler ED, editor. *Neuroimaging II: Clinical Applications*. New York: Plenum Press, pp 73-125.
- Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL, Beyreuther K (1985): Amyloid plaque core protein in Alzheimer disease and Down syndrome. *Proc Nat Acad Sci U S A* 82:4245-4249.
- McGuffin P, Owen MJ, Farmer AE (1995): Genetic basis of schizophrenia. *Lancet* 346:678-682.
- McLean SD, Saal HM, Spinner NB, Emanuel BS, Driscoll DA (1993): Velo-cardio-facial syndrome: intrafamilial variability of the phenotype (review). *Am J Dis Child* 147:1212-1216.

- Meinecke P, Beemer FA, Schinzel A, Kushnick T (1986): The velo-cardio-facial (Shprintzen) syndrome: clinical variability in eight patients. *Eur J Pediatr* 145:539-544.
- Mingarelli R, Digilio MC, Mari A, et al (1996): The search for hemizyosity at 22q11 in patients with isolated cleft palate. *J Craniofac Genet Dev Biol* 16:118-121.
- Mitnick RJ, Bello JA, Golding-Kushner KJ, Argamaso RV, Shprintzen RJ (1996): The use of magnetic resonance angiography prior to pharyngeal flap surgery in patients with velocardiofacial syndrome. *Plast Reconstr Surg* 97:908-919.
- Mitnick RJ, Bello JA, Shprintzen RJ (1994): Brain anomalies in velo-cardio-facial syndrome. *Am J Med Genet* 54:100-106.
- Moldin SO, Gottesman II (1997): Genes, experience, and chance in schizophrenia—positioning for the 21st century. *Schizophr Bull* 23:547-561.
- Monaco G, Pignata C, Rossi E, Mascellaro O, Cocozza S, Ciccimarra F (1991): DiGeorge anomaly associated with 10p deletion. *Am J Med Genet* 39:215-216.
- Morrow B, Goldberg R, Carlson C, et al (1995): Molecular definition of the 22q11 deletions in velo-cardio-facial syndrome. *Am J Hum Genet* 56:1391-1402.
- Motzikin B, Marion R, Goldberg R, Shprintzen R, Saenger P (1993): Variable phenotypes in velocardiofacial syndrome with chromosomal deletion. *J Pediatr* 123:406-410.
- Murphy KC, Jones RG, Griffiths E, Thompson PW, Owen MJ (1998): Chromosome 22q11 deletions. An under-recognised cause of idiopathic learning disability. *Brit J Psychiatry* 172:180-183.
- Murphy KC, Owen MJ (1997): The behavioural phenotype in velo-cardio-facial syndrome. *Am J Hum Genet* 61:A5.
- Murray R, Lewis SW, Revcly AM (1985): Towards an aetiological classification of schizophrenia. *Lancet* i:1023-1026.
- Murray RM, Lewis SW (1987): Is schizophrenia a neurodevelopmental disorder? *Brit Med J* 295:681-682.
- Nickel RE, Pillers DAM, Merckens M, et al (1994): Velo-cardio-facial syndrome and DiGeorge sequence with meningomyelocele and deletions of the 22q11 region. *Am J Med Genet* 52:445-449.
- O'Callaghan E, Larkin C, Kinsella A, Waddington JL (1991): Familial, obstetric, and other clinical correlates of minor physical anomalies in schizophrenia. *Am J Psychiatry* 148:479-483.
- Papoulos DF, Faedda GL, Veit S, et al (1996): Bipolar spectrum disorders in patients diagnosed with velo-cardio-facial syndrome: does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? *Am J Psychiatry* 153:1541-1547.
- Pinto-Escalante D, Ceballos-Quintal JM, Castillo-Zapata I, Cantó-Herrera J (1998): Full mosaic monosomy 22 in a child with DiGeorge syndrome facial appearance. *Am J Med Genet* 76:150-153.
- Pizzuti A, Novelli G, Ratti A, et al (1997): UFD1L, a developmentally expressed ubiquitination gene, is deleted in CATCH 22 syndrome. *Hum Mol Genet* 6:259-265.
- Propping P, Nothen MM (1995): Schizophrenia: genetic tools for unraveling the nature of a complex disorder. *Proc Natl Acad Sci U S A* 92:7607-7608.
- Puiver AE, Nestadt G, Goldberg R, et al (1994): Psychotic illness in patients diagnosed with velo-cardio-facial syndrome and their relatives. *J Nerv Ment Dis* 182:476-478.
- Ravnan JB, Chen E, Golabi M, Lebo RV (1996): Chromosome 22q11.2 microdeletions in velocardiofacial syndrome patients with widely variable manifestations. *Am J Med Genet* 66:250-256.
- Russell AJ, Munro JC, Jones PB, Hemsley DR, Murray RM (1997): Schizophrenia and the myth of intellectual decline. *Am J Psychiatry* 154:635-639.
- Ryan AK, Goodship JA, Wilson DI, et al (1997): Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. *J Med Genet* 34:798-804.
- Scambler PJ, Kelly D, Lindsay E, et al (1992): Velo-cardio-facial syndrome associated with chromosome 22 deletions encompassing the DiGeorge locus. *Lancet* 339:1138-1139.
- Schizophrenia Collaborative Linkage Group for Chromosome 22 (1998): A transmission disequilibrium and linkage analysis of D2S278 marker alleles in 574 families: further support for a susceptibility locus for schizophrenia at 22q12. *Schizophr Res* 32:115-121.
- Sedlackova E (1967): The syndrome of the congenitally shortened velum the dual innervation of the soft palate. *Folia Phoniatrica* 19:441-450.
- Shprintzen RJ, Goldberg R, Golding-Kushner KJ, Marion RW (1992): Late-onset psychosis in the velo-cardio-facial syndrome (letter). *Am J Med Genet* 42:141-142.
- Shprintzen RJ, Goldberg RB, Lewin ML, et al (1978): A new syndrome involving cleft palate, cardiac anomalies, typical facies, and learning disabilities: velo-cardio-facial syndrome. *Cleft Palate J* 15:56-62.
- Shprintzen RJ, Goldberg RB, Young D, Wolford L (1981): The velo-cardio-facial syndrome: a clinical and genetic analysis. *Pediatrics* 67:167-172.
- Sirotkin H, Morrow B, DasGupta R, et al (1996): Isolation of a new clathrin heavy chain gene with muscle-specific expression from the region commonly deleted in velo-cardio-facial syndrome. *Hum Mol Genet* 5:617-624.
- Sirotkin H, O'Donnell H, DasGupta R, et al (1997): Identification of a new human catenin gene family member (ARVCF) from the region deleted in velo-cardio-facial syndrome. *Genomics* 41:75-83.
- Sutherland HF, Wadey R, McKie JM, et al (1996): Identification of a novel transcript disrupted by a balanced translocation associated with DiGeorge syndrome. *Am J Hum Genet* 59:23-31.
- Swillen A, Devriendt K, Legius E, et al (1997): Intelligence and psychosocial adjustment in velocardiofacial syndrome: a study of 37 children and adolescents with VCFS. *J Med Genet* 34:453-458.
- Takahashi K, Kido S, Hoshino K, Ogawa K, Ohashi H, Fukushima Y (1995): Frequency of a 22q11 deletion in patients with conotruncal cardiac malformations: a prospective study. *Eur J Pediatr* 154:878-881.
- Thomas IT, Frias JL (1987): The heart in selected congenital malformations a lesson in pathogenetic relationships. *Ann Clin Lab Sci* 17:207-210.
- Turk J, Hill P (1995): Behavioural phenotypes in dysmorphic syndromes. *Clin Dysmorphol* 4:105-115.

## 22q11 Deletion Syndrome

BIOL PSYCHIATRY  
1999;46:882-891

891

- Turner TH (1989): Schizophrenia and mental handicap: a historical review, with implications for further research. *Psychol Med* 19:301-314.
- Weinberger DR (1987): Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 44:660-669.
- Weinberger DR (1997): The biological basis of schizophrenia: new directions. *J Clin Psychiatry* 58:22-27.
- Winter RM (1996): What's in a face? *Nature Genet* 12:124-129.
- Wisniewski KE, Wisniewski HM, Wen GY (1985): Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Ann Neurol* 17:278-282.
- Yamagishi H, Ishii C, Maeda J, et al (1998): Phenotypic discordance in monozygotic twins with 22q11.2 deletion. *Am J Med Genet* 78:319-321.
- Yan W, Jacobsen LK, Krasnewich DM, et al (1998): Chromosome 22q11.2 interstitial deletions among childhood-onset schizophrenics and "multidimensionally impaired." *Am J Med Genet* 81:41-43.
- Zipursky RB, Lambe EK, Kapur S, Mikulis DJ (1998): Cerebral gray matter volume deficits in first episode psychosis. *Arch Gen Psychiatry* 55:540-546.
- Zipursky RB, Lim KO, Sullivan EV, Brown BW, Pfefferbaum A (1992): Widespread cerebral gray matter volume deficits in schizophrenia. *Arch Gen Psychiatry* 49:195-205.